Frontiers in Neuroendocrinology 75 (2024) 101156

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review article

Effect of 5-alpha reductase inhibitors in animal models of Parkinson's disease

Mélanie Bourque [a], Marc Morissette [a], Amandine Isenbrandt [a,b], Silvia Giatti [c], Roberto Cosimo Melcangi [c], Manolo Carta [d], Roberto Frau [d], Marco Bortolato [e], Denis Soulet [a,b], Thérèse Di Paolo [a,b,*]

[a] Axe Neurosciences, Centre de recherche du CHU de Québec-Université Laval, Québec, QC, Canada
[b] Faculty of Pharmacy, Laval University, Quebec, QC, Canada
[c] Department of Pharmacological and Biomolecular Sciences, Center of Excellence on Neurodegenerative Diseases, Università degli Studi di Milano, Milan, Italy
[d] Department of Biomedical Sciences, "Guy Everett Laboratory", University of Cagliari, Cittadella Universitaria SP 8, Monserrato 09042, Italy
[e] Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, 30 S 2000 E, Salt Lake City, UT 84112, USA

ARTICLE INFO

Keywords:
Parkinson's disease
Dopamine
5alpha-reductase
Finasteride
Dutasteride
Neuroprotection
Dyskinesia
Brain
Gut
Inflammation

ABSTRACT

Parkinson's disease (PD) is characterized by motor symptoms due to loss of brain dopamine and non-motor symptoms, including gastrointestinal disorders. Although there is no cure for PD, symptomatic treatments are available. L-Dopa is the gold standard PD therapy, but most patients develop dyskinesias (LID), which are challenging to manage. Amantadine is recognized as the most effective drug for LID, but its adverse effects limit the use in patients. Here we review how 5α-reductase inhibitors (5ARIs), drugs used to treat benign prostatic hyperplasia and alopecia, exhibit beneficial effects in PD animal models. 5ARIs show neuroprotective properties in brain and gut dopaminergic systems, and reduce dyskinesias in rodent model of PD. Additionally, the 5ARI finasteride dampened dopaminergic-induced drug gambling in PD patients. Neuroprotection and antidyskinetic activities of 5ARIs in animal models of PD suggest their potential repurposing in men with PD to address gut dysfunction, protect brain DA and inhibit dyskinesias.

1. Introduction

1.1. Parkinson's disease

Progressive death of dopamine (DA) neurons in the substantia nigra characterize Parkinson's disease (PD) (Armstrong and Okun 2020). This leads to nigrostriatal dysfunction of the basal ganglia and the appearance of clinical symptoms such as resting tremor, rigidity, postural instability, and bradykinesia (Armstrong and Okun 2020). Non-motor symptoms such as gastrointestinal symptoms, depression, urinary dysfunction, and sleep behavior disorder are also present in PD (Armstrong and Okun 2020).

The prevalence of PD increases more than other neurological disorders (Group, 2017), and this is expected to continue increasing in future years, due to aging of the general population (Bach et al., 2011; Rossi et al., 2018). There is no cure for PD; symptomatic treatments aimed at replacing the loss of DA are used, and L-Dopa remains the gold standard as it provides the best motor improvements (Armstrong and Okun 2020). As the disease progresses, the effectiveness of symptomatic treatments decreases, and motor complications (such as motor fluctuations and L-Dopa-induced dyskinesias (LID)) appear and interfere with quality of life (Armstrong and Okun 2020). Thus, it is essential to identify preventive approaches and develop new PD treatments.

Aging is the leading risk factor for PD, and although idiopathic and familial forms of PD are described, the cause of the majority of PD cases is undetermined and involves an interaction between genetic, epigenetic, and environmental risk factors (Jankovic and Tan 2020). Sex differences are reported for PD, including incidence and prevalence, motor and non-motor symptoms, response to treatment, disease progression, and motor complications (reviewed in detail in: (Cerri et al., 2019; Jurado-Coronel et al., 2018)). Men are more predisposed to the disease than women, with a 1.5 male-to-female ratio (Collaborators

* Corresponding author at: Axe neurosciences, Centre de recherche du CHU de Québec-Université Laval, 2705 Laurier Boulevard, Quebec City, QC G1V 4G2, Canada.
E-mail address: therese.dipaolo@crchudequebec.ulaval.ca (T. Di Paolo).

https://doi.org/10.1016/j.yfrne.2024.101156
Received 3 June 2024; Received in revised form 12 September 2024; Accepted 27 September 2024
Available online 29 September 2024

2019; Hirsch et al., 2016). Women experience more often wearing-off than men and have an almost 3-fold higher risk for developing LID (Bjornestad et al., 2016; Colombo et al., 2015). Age at onset of PD is about two years older in women than men (Haaxma et al., 2007; Twelves et al., 2003), but others have not observed this (Baba et al., 2005; Frentzel et al., 2017). Women are reported to present more frequently a tremor-dominant PD phenotype, which was associated with a slower evolution of the disease, while men experience more rigidity (Baba et al., 2005; Haaxma et al., 2007).

Risk and protective factors for PD are reported to differ between men and women (Savica et al., 2013). These differences might be related to different exposure to risk or protective factors between men and women (Savica et al., 2013). It could also be due to a sex-dependent dimorphic brain development that changes its vulnerability to environmental factors and, in women, to a protective effect of sex hormones and genes located on the sex chromosomes (Savica et al., 2013). Thus, this strongly suggests that a beneficial effect of female gonadal hormones and a more prolonged exposure to circulating endogenous ovarian hormone levels throughout a woman's life may have a positive influence on PD risk.

The neuroprotective effect of sex steroids, particularly 17β-estradiol and progesterone, in animal models of PD, as well as the effect of endogenous and exogenous sex steroids on PD risk in human studies (see (Bourque et al., 2024) for review) support the use of neuroactive steroids as a therapeutic strategy for PD. Further, neuroactive steroids have multiple functions acting on, among others, mitochondria, glial cells, ion channels, and neurotransmitter systems (Bourque et al., 2024; Giatti et al., 2019b), which makes neuroactive steroids an attractive therapeutic approach for PD, as they target many functions that are affected in PD.

An alternative strategy to the use of neuroactive steroids, which are highly metabolized following oral administration, is to modulate their synthesis or metabolism. Steroidogenesis enzymes are present in the brain (Melcangi et al., 2008). 5α-reductase enzymes metabolize testosterone into dihydrotestosterone (DHT) and progesterone into 5α-dihydroprogesterone (Fig. 1) (Giatti et al., 2020). Finasteride and dutasteride are 5α-reductase inhibitors (5ARIs) used in humans to treat benign prostatic hyperplasia (Loughlin 2021) and androgenic alopecia (finasteride only) (Gupta et al., 2024). A previous case report in two PD male patients described that finasteride treatment attenuated pathological gambling symptoms induced by dopaminergic medication (Bortolato et al., 2012). Thus, this suggests that 5ARIs modulate the brain dopaminergic system, and several other studies have been carried out to investigate the role of these inhibitors in neuroprotection and motor complications caused by dopaminergic drugs.

Here, we review the effect of 5ARIs in neuroprotection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced toxicity of striatal DA neurons and myenteric plexus in mice. We also review the effect of dutasteride and finasteride on LID in 6-hydroxydopamine (6-OHDA) lesioned rats and present the mechanisms implicated in the effect of finasteride and dutasteride.

1.2. 5α-reductase enzymes and inhibitors

The NADPH-dependent enzyme 5α-reductase metabolizes testosterone into DHT and also catalyzes the conversion of progesterone into 5α-dihydroprogesterone (Fig. 1) (Giatti et al., 2020). 5α-reductase type 1 is highly expressed in brain regions with high white matter, and the enzyme is present in oligodendrocytes, neurons, Schwann cells, microglia, and astrocytes (Giatti et al., 2020). 5α-reductase type 2 is expressed in neurons and oligodendrocytes but not glial cells (Castelli et al., 2013; Giatti et al., 2020). Thus, this suggests that these isoforms have distinct functions in regulating neuroendocrine processes. There is also a third type of this enzyme, 5α-reductase type 3, which is involved in the N-linked glycosylation of proteins (Cantagrel et al., 2010), and its role in steroid metabolism is not well documented (Cantagrel et al., 2010; Uemura et al., 2008).

Finasteride and dutasteride are 5ARIs approved for benign prostatic hyperplasia and androgenic alopecia (finasteride only) (Gupta et al., 2024; Loughlin 2021). Finasteride inhibits selectively 5α-reductase type 2 and decreases serum DHT by 70 % (Clark et al., 2004). Dutasteride has a higher potency than finasteride in inhibiting both types 1 and 2, lowering serum DHT by approximately 90 % (Clark et al., 2004).

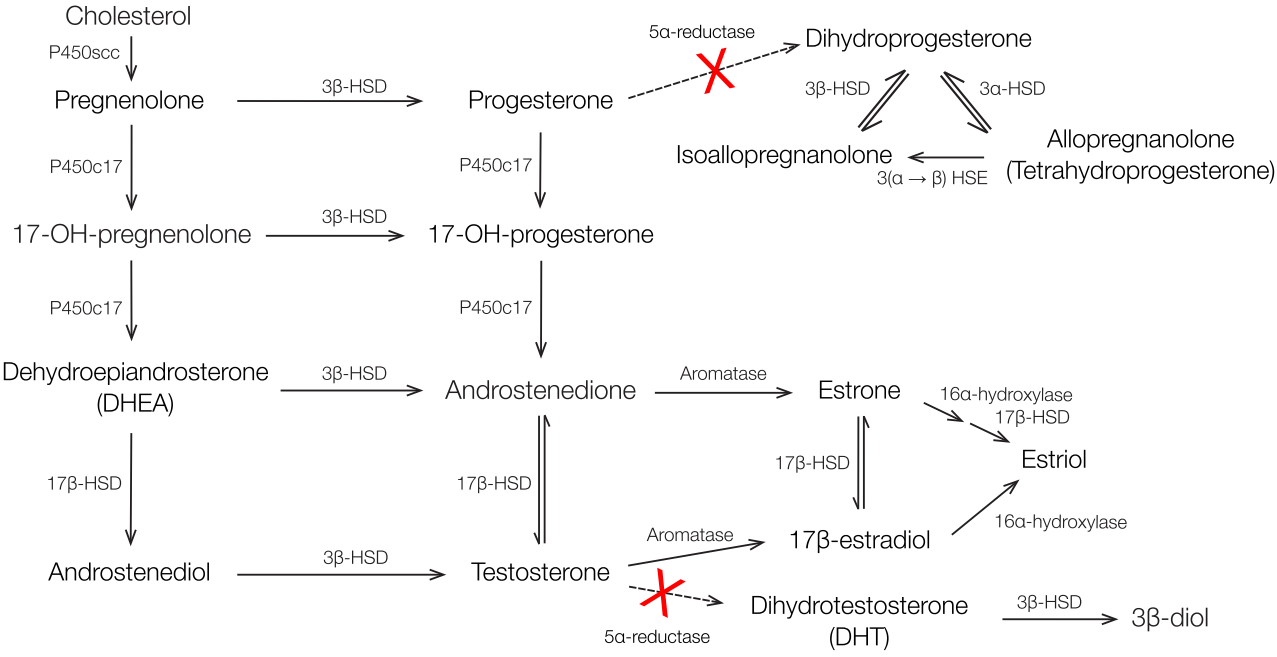

Fig. 1. Schematic representation of steroidogenesis. The 5α-reductase enzyme metabolizes testosterone to dihydrotestosterone and also catalyzes the conversion of progesterone to 5α-dihydroprogesterone. Finasteride and dutasteride inhibit the 5α-reductase enzyme, thereby blocking the conversion of testosterone to dihydrotestosterone and progesterone to dihydroprogesterone. X = inhibition.

2. Animal studies, 5α-reductase inhibitors, and brain neuroprotection

2.1. Neuroprotection of DA markers

The only study investigating the neuroprotective effect of finasteride reports that finasteride treatment in male mice was ineffective in protecting dopaminergic neurons from MPTP toxicity (Table 1) (Litim et al., 2015). Dutasteride administered before and pursued after MPTP prevented MPTP-induced loss of DA markers in male mice (Table 2) (Isenbrandt et al., 2021; Litim et al., 2015; Litim et al., 2017). When investigating if dutasteride can rescue DA neurons from MPTP toxicity in male mice, no effect is observed when dutasteride is started only after MPTP (Litim et al., 2017).

Male mice are more vulnerable to MPTP toxicity than female mice (Isenbrandt et al., 2021). Gonads intact female mice had little or no effect of MPTP on DA markers, consistent with a neuroprotective effect of endogenous female sex hormones (Miller et al., 1998). Thus, the sex difference observed in PD is also presented in the MPTP mice model. The endogenous protection observed in female mice is lost upon ovariectomy, and these mice show altered DA markers following MPTP injury, whereas gonadectomy in male mice does not change MPTP toxicity (Isenbrandt et al., 2021). Thus, female mice with intact gonads benefit from endogenous protection against MPTP, and dutasteride treatment neither adds nor modifies this protection (Isenbrandt et al., 2021). On the contrary, ovariectomized (OVX) female mice show MPTP-induced loss of DA markers similar to male mice, and dutasteride treatment is not neuroprotective in both gonadectomized (GDX) male and female mice (Isenbrandt et al., 2021).

2.2. Mechanisms of action

2.2.1. Effect on MPTP metabolism

The sex difference reported in MPTP toxicity is not due to metabolic/pharmacokinetic differences of MPTP since striatal 1-methyl-4-phenylpyridinium (MPP^+) contents are similar between males and females,

Table 1
Effect of finasteride on dopaminergic activity in Parkinson's disease (PD) and animal models of PD.

Human study Study description	Dose and duration	Species and age	Toxin	Main result	Reference
Case reports of two PD patients with pathological gambling.	5 mg/day for several weeks.			Attenuated pathological gambling symptoms of PD patients.	(Bortolato et al., 2012)
Animal studies **Aim of the study**	**Dose and duration**	**Species and age**	**Toxin**	**Effect**	**Reference**
Neuroprotection studies					
Investigation of protection against MPTP induced lesion of the dopaminergic nigrostriatal pathway.	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	No protection of striatal DA, DOPAC and HVA contents; DAT and VMAT2 specific binding.	(Litim et al., 2015)
L-Dopa-induced dyskinesias studies (LID)					
Investigation of its *acute* effect on LID in dyskinetic animals.	30 and 60 mg/kg once daily for one day.	Male rats, dyskinetic	6-OHDA	LID decreased with the dose of 60 mg/kg, no effect with the 30 mg/kg dose.	(Frau et al., 2017b)
Investigation of its *chronic* effect on LID in dyskinetic animals.	30 and 60 mg/kg once daily for three weeks.	Male rats, dyskinetic	6-OHDA	LID decreased with the dose of 60 mg/kg at all time point; the 30 mg/kg dose became effective upon prolonged administration.	(Frau et al., 2017b)
Investigation of its *chronic* effect on LID in dyskinetic animals.	30 and 60 mg/kg once daily for three weeks.	Female rats (gonads intact), dyskinetic	6-OHDA	LID decreased with the dose of 60 mg/kg.	(Frau et al., 2017b)
Investigation of its *chronic* effect on prevention of LID development.	30 and 60 mg/kg once daily in co-treatment with L-Dopa for 24 days.	Male rats, L-Dopa naïve	6-OHDA	**Anti-dyskinetic effect:** −Main effect of treatment with the dose of 60 mg/kg to decrease the development of LID. **Impaired L-Dopa motor activation:** −Partial reduction of forelimb use was observed at 60 mg/kg at day 1 but not day 24.	(Frau et al., 2017b)
Investigation of its *chronic* effect to prevent LID development.	30 and 60 mg/kg once daily for three weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Male rats, L-Dopa naïve	6-OHDA	Both doses decrease the development of LID.	(Frau et al., 2017b)
Investigation of its *chronic* effect to prevent LID development.	30 and 60 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats; L-Dopa naïve	6-OHDA	**Anti-dyskinetic effect:** −Both doses decreased development of LID. **Impaired L-Dopa motor activation:** −Partial reduction of forelimb use is observed at 60 mg/kg at day 1 but not day 23. −Reduced motor activation induced by L-Dopa treatment.	(Fanni et al., 2019)
Peripheral effects					
Investigation of protection against MPTP induced lesion of myenteric plexus.	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks)	MPTP	12.5 mg/kg but not 5 mg/kg prevented MPTP-induced DA and vasoactive intestinal peptide neurons damage in the myenteric plexus.	(Poirier et al., 2022)

DA, dopamine; DAT, dopamine transporter; DOPAC, 3,4-dihydrophenylacetic acid; HVA, homovanillic acid; LID; L-Dopa-induced dyskinesias, MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Parkinson's disease; 6-OHDA, 6-hydroxydopamine.

Table 2
Effect of dutasteride on dopaminergic activity in animal models of PD.

Animal studies Aim of the study	Dose and duration	Species and age	Toxin	Effect	Reference
Neuroprotection studies					
Investigation of protection against MPTP induced lesion of the dopaminergic nigrostriatal pathway.	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	Protection of striatal DA, DOPAC and HVA contents; DAT and VMAT2 specific binding.	(Litim et al., 2015; Litim et al., 2017)
Investigation of rescue of DA neurons from MPTP toxicity.	5, 12.5 and 25 mg/kg one hour before the first and one hour after the last MPTP injection, and then once daily for 5 days.	Male mice (10 weeks, gonads intact)	MPTP	No protection of striatal DA, DOPAC and HVA contents.	(Litim et al., 2017)
Investigation of protection against MPTP induced lesion of the dopaminergic nigrostriatal pathway and the impact of hormonal status.	5 mg/kg once daily for 10 days.	Male mice (17 weeks, GDX and gonads intact)	MPTP	Protection of striatal DA, DOPAC and HVA contents, DAT and VMAT2 specific binding in gonads intact but not in GDX mice.	(Isenbrandt et al., 2021)
Investigation of protection against MPTP induced lesion of the dopaminergic nigrostriatal pathway and the impact of hormonal status.	5 mg/kg once daily for 10 days.	Female mice (17 weeks, OVX and gonads intact)	MPTP	Gonads intact female mice had little or no effect of MPTP on DA markers. No effect of dutasteride observed in OVX mice.	(Isenbrandt et al., 2021)
L-Dopa-induced dyskinesias studies					
Investigation of its *chronic* effect to prevent LID development.	15 and 30 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats; L-Dopa naïve	6-OHDA	**Anti-dyskinetic effect:** −Both doses decreased development of LID. **Effect on L-Dopa motor activation:** − Did not modify the improvement of forelimb use induced by L-Dopa. − Did not change the motor activation induced by L-Dopa treatment.	(Fanni et al., 2019)
Investigation of its *chronic* effect to prevent LID development.	15 mg/kg once daily one day before L-Dopa initiation then in co-treatment with L-Dopa for three weeks.	Male rats, L-Dopa naïve	6-OHDA	**Anti-dyskinetic effect:** − Decreased development of LID. **Effect on L-Dopa motor activation:** − Did not modify improvement of forelimb use induced by L-Dopa. − Did not change motor activation induced by L-Dopa treatment.	(Corsi et al., 2023)
Peripheral effects					
Investigation of protection against MPTP induced lesion of myenteric plexus.	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	5 mg/kg but not 12.5 mg/kg prevented MPTP-induced DA and vasoactive intestinal peptide neurons damage in the myenteric plexus.	(Poirier et al., 2022)

DA, dopamine; DAT, dopamine transporter; DOPAC, 3,4-dihydrophenylacetic acid; GDX, gonadectomized; HVA, homovanillic acid; LID; L-Dopa-induced dyskinesias, MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; OVX, ovariectomized; VMAT2, vesicular monoamine transporter 2; 6-OHDA, 6-hydroxydopamine.

regardless of hormonal status (intact gonads or GDX) (Isenbrandt et al., 2021). Furthermore, dutasteride treatment does not alter striatal MPP^+ content, so the sex difference observed in the effect of dutasteride is not caused by a change in MPTP metabolism (Isenbrandt et al., 2021).

2.2.2. *Effect on brain steroid levels*

5α-reductase is responsible for the conversion of testosterone to DHT and progesterone into 5α-dihydroprogesterone (Fig. 1) (Giatti et al., 2020); its inhibition would be expected to increase the levels of testosterone and progesterone. Levels of 17β-estradiol could then be increased via aromatization of testosterone. Inhibiting the conversion of testosterone to DHT leads to decreased levels of DHT, a steroid reported having no neuroprotective effect when administered in MPTP-treated male mice and 6-OHDA-lesioned GDX female and male rats (Ekue et al., 2002; Gillies et al., 2004; Murray et al., 2003). Progesterone has a neuroprotective effect in MPTP male mice (Bourque et al., 2016). While testosterone lacks a beneficial effect (Dluzen 1996; Ekue et al., 2002), it can be converted by aromatization to 17β-estradiol, which is known to be neuroprotective in both males and females (Bourque et al., 2024).

Results from our previous study showed, as expected, a decrease in brain and plasma levels of DHT and 5α-dihydroprogesterone in male mice with dutasteride treatment (Litim et al., 2017). Brain and plasma 17β-estradiol levels remain very low following MPTP and/or dutasteride treatment of male mice, suggesting the neuroprotective effect of dutasteride is not obtained by an increase in 17β-estradiol levels (Litim et al., 2017). Alternatively, a possible regional increase in 17β-estradiol levels may have been diluted in the sample comprised of one brain hemisphere. Plasma and brain progesterone levels from male mice receiving only dutasteride were unchanged. MPTP increased the levels of progesterone, whereas the levels were lower in MPTP male mice treated with dutasteride (Litim et al., 2017).

Dutasteride and/or MPTP also affected testosterone and DHT levels in brain and plasma. Mice treated with MPTP exhibited lower levels of testosterone and DHT in brain and plasma, aligning with previous findings conducted in the MPTP model and PD patients (Nitkowska et al., 2015; Okun et al., 2004). As expected, dutasteride reduced DHT levels in intact mice, and counteracted the reductions in testosterone levels caused by MPTP. While dutasteride did not directly raise testosterone levels, maintaining its normal physiological levels may be one of the mechanisms by which dutasteride prevented the MPTP-induced toxicity. This suggests that brain levels of testosterone (progesterone, and 17β-estradiol) alone cannot simply explain the neuroprotective effects of dutasteride in male mice. However, as these neurosteroids were measured across the whole brain, and steroid levels can significantly vary among different brain regions (Caruso et al., 2010; Caruso et al., 2013), this may not accurately reflect the specific changes occurring in critical areas involved in PD pathogenesis, such as striatum and substantia nigra.

In MPTP mice we showed increased plasma progesterone and allopregnanolone levels in MPTP lesioned male mice compared to intact

controls while in the brain of these mice pregnenolone, progesterone and its metabolites 5α-dihydroprogesterone, isoallopregnanolone and allopregnanolone were increased (Litim et al., 2017). Interestingly in a recent study where 27 steroids were measured, only the progesterone metabolism pathway (not the estradiol nor the testosterone pathways) was shown to change in the substantia nigra of PD patients (Luchetti et al., 2023). These authors showed an increase of the progesterone metabolites (allopregnanolone and 3α5α20α-hexahydroprogesterone) in the substantia nigra from male and female patients at early stages of PD, suggesting that the upregulation of allopregnanolone may represent a potential protective effect at the beginning of the disease. These changes of steroids in the substantia nigra from PD patients show similarities with the changes we observed in the brain and plasma of MPTP mice (Litim et al., 2017).

MPTP male mice treated with dutasteride are protected from MPTP only when gonads are intact, suggesting that the loss of hormones from GDX impacts the neuroprotective effect of dutasteride (Isenbrandt et al., 2021). Changes in neurosteroid and enzyme levels are observed following GDX in both male and female mice. In the cerebral cortex, long-term OVX increases pregnenolone levels in female mice while progesterone and its metabolite dihydroprogesterone were decreased (Caruso et al., 2010). In male mice, dihydroprogesterone, allopregnanolone, dehydroepiandrosterone (DHEA), testosterone, and DHT levels in the cerebral cortex were lower in GDX mice than in those with intact gonads (Caruso et al., 2010). In the cerebral cortex, mRNA levels of the enzyme 5α-reductase type 1 are higher in GDX male and female mice (Giatti et al., 2019a). While there are regional differences in steroid levels and no data are available concerning the impact of GDX on steroid levels in the striatum, it is suggested that the levels of steroids present influence the effect of dutasteride.

2.2.3. *Microglia and astrocytes*

The nigrostriatal system shows sex-associated morphological and/or functional changes in microglia, and these sex differences could be involved in the different profiles of development and clinical course of PD between males and females (Bourque et al., 2023). Young and adult male and female mice show similar striatal microglia density and morphology (Guneykaya et al., 2018), and gonadectomy does not modify these parameters (Isenbrandt et al., 2023). Microglia doublets happen after the division of microglia cells during their proliferation process. The density of striatal microglia doublets is similar between gonads intact males, gonads intact, and OVX females, whereas GDX males had a higher density (Isenbrandt et al., 2023). Microglia in the midbrain were found to have a different transcriptional profile than in the striatum and prefrontal cortex (Barko et al., 2022). Midbrain microglia showed a more immune-vigilant transcriptional profile, whereas microglia transcriptional profile from the striatum and prefrontal cortex was linked to genes involved in synaptic remodeling and neuronal architecture (Barko et al., 2022). Male microglia show a more inflammatory profile, while synapse-related transcripts and associated pathways (glutamatergic synapse and gamma-aminobutyric acid (GABA) receptor binding) were higher in females but only in the midbrain (Barko et al., 2022).

Microglia, the resident macrophage of the brain, and astrocytes, which play various roles in brain function, become dysfunctional in PD (Awogbindin et al., 2020; Wang et al., 2023). In MPTP-lesioned mice, striatal glial fibrillary acidic protein (GFAP) levels are increased in male mice (gonads intact and GDX) and OVX females, whereas gonads intact females show no change (Isenbrandt et al., 2021). Dutasteride treatment reduced the increase in striatal GFAP levels induced by MPTP only in gonads intact male mice (Table 3) (Isenbrandt et al., 2021; Litim et al., 2017). No change in GFAP levels in substantia nigra is reported following the MPTP lesion (Isenbrandt et al., 2021). In male mice (both gonads intact and GDX), MPTP induced change in microglia morphology from a quiescent to an activated phenotype with fewer arborized and shorter ramifications, whereas microglia morphology is not changed by MPTP in female mice (Isenbrandt et al., 2023). Dutasteride does not affect morphological change induced by MPTP in male mice (Isenbrandt et al., 2023). MPTP male mice have a higher microglia doublets density, and dutasteride prevented this increase induced by MPTP in gonads intact but not GDX male mice (Isenbrandt et al., 2023). In female mice, microglia doublets were not different following OVX, MPTP, or dutasteride treatment (Isenbrandt et al., 2023). Increased microglia density is only observed in male mice (both gonads intact and GDX) lesioned with MPTP, suggesting that microglia from females are less susceptible to MPTP, independently of hormonal status (Isenbrandt et al., 2023). Dutasteride treatment prevents this increase in gonads intact but not in GDX male mice (Isenbrandt et al., 2023). Thus, microglia were not affected by MPTP in OVX and gonads intact female mice, suggesting gonadal hormone-independent mechanisms.

2.2.4. *Cell survival signaling pathways*

Akt and its downstream substrate glycogen synthase kinase 3β (GSK3β), and extracellular signal-regulated kinases 1/2 (ERK), are signaling pathways involved in 17β-estradiol neuroprotection (Bourque et al., 2012; Bourque et al., 2015; D'Astous et al., 2006). It was hypothesized that dutasteride, since the metabolism of testosterone to DHT was inhibited, would induce an increase in 17β-estradiol levels which would activate the cellular Akt/GSK3β and ERK1/2 pathways. However, dutasteride did not modify 17β-estradiol levels (Litim et al., 2017). Dutasteride did not change phosphorylation levels of Akt, GSK3β and ERK1/2 in the striatum (Litim et al., 2017), suggesting that the neuroprotective effect of dutasteride involves other cellular mechanisms.

3. Animal studies, 5α-reductase inhibitors and gut neuroprotection

Non-motor symptoms are observed in PD many years before the onset of motor symptoms and most of PD patients will experience gastrointestinal symptoms such as constipation (Thomasi et al., 2024). α-synuclein aggregates are found in the gastrointestinal tract before the onset of motor symptoms, suggesting that PD pathology could initiate in the periphery and propagate to the central nervous system (Braak et al., 2003a; Braak et al., 2003b; Sánchez-Ferro et al., 2015).

Previous studies have shown the involvement of the innate immune system in the alteration of DA neurons in the myenteric plexus of MPTP-lesioned mice (Côté et al., 2015; Poirier et al., 2016). In gonads intact male mice, finasteride 12.5 mg/kg but not 5 mg/kg prevented MPTP-induced DA and vasoactive intestinal peptide neuron damage in the myenteric plexus, while for dutasteride only the 5 mg/kg dose showed protection (Tables 1 and 2) (Poirier et al., 2022). Following MPTP, macrophages will infiltrate the myenteric plexus, producing an activation of the innate immune response (Côté et al., 2015). The increase in enteric macrophage density following MPTP and activation of proinflammatory monocytes play a role in the loss of tyrosine hydroxylase expression in neurons in the myenteric plexus (Côté et al., 2015). Dutasteride treatment prevented the increase in macrophage density, while this was partially reduced with the dose of 12.5 mg/kg of finasteride (Tables 3 and 4) (Poirier et al., 2022). Proinflammatory macrophages express higher levels of the major histocompatibility complex (MHC) class II (MHCII) receptors (Conrad and Dittel 2011). The density of MHCII receptors is increased in MPTP mice, and this is prevented by dutasteride, while the effect of finasteride is inconclusive (Poirier et al., 2022). Higher levels of proinflammatory cytokines are found in the colon of PD patients and correlate with the progression of the disease (Bellini et al., 2023; Devos et al., 2013). *In vitro* work was done with MPP^+, the active metabolite of MPTP, to investigate the anti-inflammatory effect of dutasteride and finasteride. Only dutasteride prevented the nuclear factor-kappa B (NF-κB) response, oxidative stress, and nitric oxide and proinflammatory cytokines production induced by MPP^+ (Poirier et al., 2022). Mitochondrial activity is impaired in PD (Matsui and Takahashi 2024) and an *in vitro* study with MPP^+ also shows

Table 3
Mechanism implicated in dutasteride neuroprotection, LID and peripheral studies.

	Dose and duration	Species and age	Toxin	Effect	Reference
Neuroprotection studies					
GFAP Akt GSK3β ERK1/2	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	Decreased MPTP-induced increase in striatal GFAP levels. No change of striatal pAkt(Ser473)/Akt, pGSK3β/GSK3β nor pERK1/2/ERK1/2 levels with MPTP and dutasteride.	(Litim et al., 2017)
GFAP	5 mg/kg once daily for 10 days.	Male mice (17 weeks, GDX and gonads intact)	MPTP	Decreased MPTP-induced increase in striatal GFAP levels in gonads intact male mice but not in GDX mice.	(Isenbrandt et al., 2021)
GFAP	5 mg/kg once daily for 10 days.	Female mice (17 weeks, OVX and gonads intact)	MPTP	No change of striatal GFAP levels with MPTP and dutasteride in gonads intact female mice. Did not decrease the MPTP-induced increases in striatal GFAP levels in OVX female mice.	(Isenbrandt et al., 2021)
Microglia (Iba1)	5 mg/kg once daily for 10 days.	Male mice (17 weeks, GDX and gonads intact)	MPTP	MPTP increased striatal microglial density that was prevented by dutasteride only in gonads intact male mice.	(Isenbrandt et al., 2023)
Microglia (Iba1)	5 mg/kg once daily for 10 days.	Female mice (17 weeks, OVX and gonads intact)	MPTP	Striatal microglia density was not different following OVX, MPTP or dutasteride treatment in female mice.	(Isenbrandt et al., 2023)
Microglial doublet	5 mg/kg once daily for 10 days.	Male mice (17 weeks, GDX and gonads intact)	MPTP	MPTP increased striatal microglial doublets that was prevented by dutasteride only in gonads intact male mice.	(Isenbrandt et al., 2023)
Microglial doublet	5 mg/kg once daily for 10 days.	Female mice (17 weeks, OVX and gonads intact)	MPTP	Striatal microglia doublets were not different following OVX, MPTP or dutasteride treatment in female mice.	(Isenbrandt et al., 2023)
Microglial morphology	5 mg/kg once daily for 10 days.	Male mice (17 weeks, GDX and gonads intact)	MPTP	MPTP changed microglia morphology from a quiescent to an activated phenotype with fewer arborized and shorter ramifications. Dutasteride has no effect in gonads intact and GDX MPTP mice.	(Isenbrandt et al., 2023)
Microglial morphology	5 mg/kg once daily for 10 days.	Female mice (17 weeks, OVX and gonads intact)	MPTP	Microglia morphology was not changed by MPTP in female mice (gonads intact and OVX).	(Isenbrandt et al., 2023)
L-Dopa-induced dyskinesias studies					
D1-D3 receptors	15 and 30 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats, L-Dopa naïve	6-OHDA	Dutasteride (both doses) reduced striatal D1-D3 receptors co-immunoprecipitation.	(Fanni et al., 2019)
D1-D3 receptors	15 mg/kg once daily one day before L-Dopa initiation then in co-treatment with L-Dopa for three weeks.	Male rats, L-Dopa naïve	6-OHDA	Dutasteride reduced striatal D1-D3 receptors co-immunoprecipitation.	(Corsi et al., 2023)
pERK1/2, pDARPP-32	15 and 30 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats, L-Dopa naïve	6-OHDA	Dutasteride (both doses) prevented the L-Dopa induced upregulation of striatal pERK1/2 and pDARPP-32.	(Fanni et al., 2019)
pERK1/2, pDARPP-32	15 mg/kg once daily one day before L-Dopa initiation then in co-treatment with L-Dopa for three weeks.	Male rats, L-Dopa naïve	6-OHDA	Dutasteride prevented the L-Dopa induced upregulation of striatal pERK1/2 and pDARPP-32.	(Corsi et al., 2023)
Peripheral effects					
MHCII receptors	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	Dutasteride prevented the increase in MHCII receptors induced by MPTP.	(Poirier et al., 2022)
NF-κB	1 μM for 24 h	Monocytic cells	MPP^+	Dutasteride prevented the induction of NF-κB response by MPP^+.	(Poirier et al., 2022)
NO, IL-1β, IL-6, oxidative stress marker CellROX	1 μM for 24 h	THP-1 cells	MPP^+	Dutasteride prevented MPP^+ increase in NO, IL-1β, IL-6 and oxidative stress marker CellROX.	(Poirier et al., 2022)
Oxidative stress production, mitochondrial membrane potential, mitochondrial basal respiration, ATP production	1 μM for 24 h	THP-1 cells	MPP^+	Dutasteride prevented the impair mitochondrial function induced by MPP^+.	(Poirier et al., 2022)

DARPP-32, dopamine- and cAMP-regulated phosphoprotein; ERK1/2, extracellular signal-regulated kinases 1/2; GFAP, glial fibrillary acidic protein; GSK3β, glycogen synthase kinase 3β; GDX, gonadectomized; Iba1, ionized calcium-binding adapter molecule 1; IL, interleukin; LID; L-Dopa-induced dyskinesias, MHCII, major histocompatibility complex class II; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB, nuclear factor-kappa B; NO, nitric oxide; OVX, ovariectomized; 6-OHDA, 6-hydroxydopamine.

Table 4
Mechanisms implicated in finasteride neuroprotection, LID and peripheral studies.

	Dose and duration	Species and age	Toxin	Effect	Reference
L-Dopa-induced dyskinesias studies					
D1-D3 receptors	15 and 30 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats, L-Dopa naïve	6-OHDA	Finasteride (both doses) reduced striatal D1-D3 receptors co-immunoprecipitation.	(Fanni et al., 2019)
pERK1/2, pDARPP-32	15 and 30 mg/kg once daily for two weeks before L-Dopa initiation then in co-treatment with L-Dopa for 24 days.	Adult male rats, L-Dopa naïve	6-OHDA	Finasteride at 30 mg/kg but not 15 mg/kg prevented the L-Dopa-induced upregulation of striatal pERK1/2 and pDARPP-32.	(Fanni et al., 2019)
Peripheral effects					
MHCII receptors	5 and 12.5 mg/kg once daily for 10 days.	Male mice (10 weeks, gonads intact)	MPTP	Finasteride did not prevent the increase in MHCII receptors induced by MPTP.	(Poirier et al., 2022)
NF-κB	1 μM for 24 h	Monocytic cells	MPP^+	Finasteride did not prevent the induction of NF-κB response by MPP^+.	(Poirier et al., 2022)
NO, IL-1β, IL-6, oxidative stress marker CellROX	1 μM for 24 h	THP-1 cells	MPP^+	Finasteride did not prevent MPP^+ increase in NO, IL-1β, IL-6 and oxidative stress marker CellROX.	(Poirier et al., 2022)
Oxidative stress production, mitochondrial membrane potential, mitochondrial basal respiration, ATP production	1 μM for 24 h	THP-1 cells	MPP^+	Finasteride did not prevent the impair mitochondrial function induced by MPP^+.	(Poirier et al., 2022)

DARPP-32, dopamine- and cAMP-regulated phosphoprotein; ERK1/2, extracellular signal-regulated kinases 1/2; IL, interleukin; LID; L-Dopa-induced dyskinesias, MHCII, major histocompatibility complex class II; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NF-κB, nuclear factor-kappa B; NO, nitric oxide; 6-OHDA, 6-hydroxydopamine.

alteration in mitochondrial function, measured by mitochondrial production of free radicals, membrane depolarization, decreased basal respiration, and ATP production (Poirier et al., 2022). These mitochondrial dysfunctions induced by MPP^+ were inhibited by dutasteride, while finasteride had no effect (Poirier et al., 2022). Thus, like the central nervous system, in the periphery dutasteride has greater efficiency than finasteride.

4. 5α-reductase inhibitors effect on L-Dopa-induced dyskinesias

Motor complications, such as LID, will be experienced by a majority of PD patients within 10 years of L-Dopa therapy (Prashanth et al., 2011). The substantial decrease in striatal DA content in PD induces alterations in other neurotransmitter systems such as an increased in glutamatergic transmission (di Biase et al., 2023). The loss of dopaminergic neurons in PD also produces a decrease in transporters (DA transporter and vesicular monoamine transporter 2), which in turn reduces the reuptake and storage of DA. L-Dopa is extremely effective during the first few years of diagnosis, but it partly loses its effect upon the progression of neurodegeneration. As the latter progresses, serotonergic neurons take over as they possess the enzymatic machinery required to convert L-Dopa to DA and store DA into synaptic vesicles. However, serotonergic neurons lack the pre-synaptic auto-receptor required to fine-tune synaptic DA release (Carta et al., 2007; Carta and Björklund 2018; di Biase et al., 2023; Kwon et al., 2022). In turn, this will lead to excessive synaptic DA release, pulsatile stimulation of DA receptors and altered DA receptors signaling cascades, ultimately leading to changes in gene transcription and protein synthesis implicated in LID (di Biase et al., 2023; Kwon et al., 2022). Beside serotonin neurons, other non-dopaminergic systems such as glutamatergic and noradrenergic systems are involved in the pathophysiology of LID (Calon et al., 2003; Morin et al., 2015; Ouattara et al., 2010; Ouattara et al., 2011; Riahi et al., 2011; Shin et al., 2014). Several alterations of electrophysiological activity of the motor cortex and basal ganglia circuitry are also associated with LID (di Biase et al., 2023).

Whereas preclinical results have been promising on the use of serotonergic or glutamatergic compounds for the treatment of LID, clinical application has been limited. There is, therefore, an unmet need for effective compounds that can treat LID without reducing the therapeutic effect of L-Dopa. The rational of using 5ARIs relies on the fact that these compounds, by modulating the neurosteroid pathways, have been shown to ameliorate hyperdopaminergic states that share some aspect with LID (Bortolato et al., 2012; Frau et al., 2013; Frau et al., 2016; Muroni et al., 2011).

In agreement with the reported ability of 5ARIs to modulate the dopaminergic system (Bortolato et al., 2008; Frau et al., 2013; Frau et al., 2016), finasteride and dutasteride have been shown to exert significant effect against LID (Tables 1 and 2). In a first study, Frau and colleagues investigated to ability of finasteride to prevent development of LID as well as to treat already established dyskinesias in 6-OHDA-lesioned rats (Frau et al., 2017b). Daily treatment with finasteride, given 40 min before L-Dopa, produced significant reduction of LID in all experimental conditions and at both tested doses, albeit the higher dose (60 mg/kg) produced a partial reduction of the L-Dopa therapeutic effect in the stepping test at the first drug exposure. The antidyskinetic effect was also observed in gonads intact female 6-OHDA-lesioned rats, but only at the higher dose tested (Frau et al., 2017b).

In a following study, the investigation was extended to dutasteride (Fanni et al., 2019). Results showed that dutasteride was as effective as finasteride in reducing both development and established LID but at half of the finasteride dose (15 mg/kg). Importantly, no reduction of the therapeutic efficacy of L-Dopa was observed in the stepping test or general motor activation.

4.1. Mechanism of action

4.1.1. Steroids levels

As presented in section 2.2.2, in the early stage of PD, the levels of allopregnanolone and its metabolite 3α5α20α-hexahydroprogesterone in substantia nigra were reported to be higher as compared to controls (Luchetti et al., 2023). However, at a more advanced stage of the disease, allopregnanolone and 5α-dihydroprogesterone levels in substantia nigra were reduced as compared to early stage of PD (Luchetti et al., 2023). This decrease in progesterone metabolites may be explained by a lower level in the 5α-reductase type 1 enzyme, which metabolizes progesterone to 5α-dihydroprogesterone, in the substantia nigra of male

and female PD patients (Luchetti et al., 2010). Dihydroprogesterone and allopregnanolone, two progesterone metabolites, are also reduced in plasma and CSF of male PD patients (di Michele et al., 2003).

In 6-OHDA lesioned male rats, striatal levels of pregnenolone and 5α-dihydroprogesterone are decreased (Melcangi et al., 2012), as well as cortical levels of 5α-dihydroprogesterone. Finasteride use in male rats increases the levels of pregnenolone and progesterone in the striatum and the prefrontal cortex (Frau et al., 2017a). Thus, since finasteride and dutasteride have antidyskinetic effects (Corsi et al., 2023; Fanni et al., 2019; Frau et al., 2017b), this suggests that the increase of pregnenolone and progesterone-induced by finasteride (Frau et al., 2017a) could be involved in the antidyskinetic effect of 5ARIs. Whereas progesterone treatment does not affect LID in already dyskinetic female MPTP monkeys (Gomez-Mancilla and Bédard 1992), pregnenolone decreased LID development in 6-OHDA male rats (Corsi et al., 2023), suggesting that pregnenolone levels increase is important in the antidyskinetic effect of 5ARIs.

No steroid receptor for pregnenolone has yet been identified but the sulfate form of this steroid acts as an allosteric modulator on $GABA_A$, N-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (Schverer et al., 2018). Pregnenolone sulfate might thus regulate the alterations of neurotransmitter systems in PD and LID. An increase in glutamate transmission has been implicated in the development of LID (Campanelli et al., 2022), and higher levels of NMDA and AMPA receptors were found in the brains of PD patients and MPTP monkeys with LID (Calon et al., 2003; Ouattara et al., 2009; Ouattara et al., 2010). In support of the role of NMDA and AMPA receptors in LID, using antagonists of NMDA or AMPA receptors reduced LID (Bourque et al., 2022; Kobylecki et al., 2010; Rajput et al., 1998). Pregnenolone sulfate has a stimulatory effect on NR2A- and NR2B-containing NMDA receptors but inhibits NR2C- and NR2D-containing NMDA receptors (Schverer et al., 2018). While pregnenolone sulfate binds both NR2B and NR2D subunits of the NMDA receptor, it has a better affinity for NR2D than NR2B (Cameron et al., 2012). NR2D is found in striatal cholinergic interneurons and striatal spiny projection neurons of 6-OHDA dyskinetic rats, and the use of NR2D antagonists decreases LID (Mellone et al., 2019).

4.1.2. *Molecular pathways*

In line with the idea that 5ARIs can modulate DA receptors signaling, finasteride and dutasteride have been shown to normalize phosphorylation of signaling molecules downstream to DA receptors, which are upregulated by chronic L-Dopa treatment in 6-OHDA-lesioned rats (Table 3 and 4) (Fanni et al., 2019). Specifically, pERK1/2 and phosphorylated DA- and cAMP-regulated phosphoprotein (pDARPP-32) levels were lower in L-Dopa-treated parkinsonian rats upon administration of either finasteride or dutasteride. Moreover, these treatments also normalized $G\alpha_{olf}$ levels (Fanni et al., 2019). Most interestingly, both finasteride and dutasteride reduced striatal D1-D3 receptors co-immunoprecipitation (Tables 3 and 4) (Corsi et al., 2023; Fanni et al., 2019), an index of heteromer formation (Marcellino et al., 2008). Abnormal striatal D1 receptor trafficking and an increase in striatal D3 receptor expression are associated with LID (Spigolon and Fisone 2018). MPTP monkeys have lower expression levels of D3 receptors, while higher levels of D3 receptors are found in dyskinetic MPTP monkeys as compared to non-dyskinetic L-Dopa-treated MPTP monkeys, and D3 receptors have been correlated with the severity of LID (Bézard et al., 2003). Thus, the overexpression of D3 receptors might further increase D1 receptor sensitization and contribute to development of LID. In support, antagonists of D3 receptors have been reported to reduce LID (Bézard et al., 2003; Chagraoui et al., 2022; Visanji et al., 2009). In light of these studies, prevention of D1-D3 receptor heteromerization would well explain the reduced phosphorylation of striatal signaling molecules reported after 5ARIs treatment (Corsi et al., 2023).

In agreement with the hypothesis that an increase in striatal pregnenolone levels might account, at least in part, for the antidyskinetic effect of 5ARIs, direct administration of pregnenolone to 6-OHDA-treated rats had the same effect as dutasteride on prevention of LID and also inhibited the increased D1-D3 receptors interaction as well as the augmented ERK1/2 and DARPP-32 phosphorylation induced by L-Dopa administration (Corsi et al., 2023).

As reviewed above, 5ARIs were as effective in counteracting established dyskinesias as they were in preventing it from emerging. This applies to both finasteride and dutasteride. A similar mechanism may therefore play a role in the two experimental approaches. However, the molecular mechanisms of the antidyskinetic effects of 5ARIs (striatal markers of LID and dopamine D1R-D3R heteromer formation) were evaluated only in the preventive treatment. Likewise, the same molecular underpinnings with the antidyskinetic effects of pregnenolone was reproduced exclusively on the prevention of dyskinesias. Exploring the molecular mechanisms of established dyskinesias is critical for clinical applicability, as it can lead to better treatment options for patients who typically already suffer from this condition. Thus, future results should clarify whether the abovementioned mechanisms of 5ARIs and pregnenolone extends to already established LID.

5. Conclusions and perspectives

The accumulating evidence reviewed here supports the beneficial role of 5ARIs in rodent models of PD at different stages of the disease. Hence, at the early stages of PD modeled with mice bearing a moderate dopaminergic nigrostriatal lesion, 5ARIs show neuroprotective activity in the brain and the gut dopaminergic systems. Afterward, at a later stage of PD modeled in mice with a more extensive dopaminergic nigrostriatal lesion and initiation of L-Dopa treatment, 5ARIs can prevent the development of LID. Subsequently, when LID is already developed, 5ARIs can inhibit the expression of LID.

This implies chronic treatment with 5ARIs for patients with PD, and their side effects should be considered. Finasteride and dutasteride have been widely used in humans for many years, with limited side effects supporting their translational value for PD and higher benefits over risks. However, as expected with the reduction of androgens (DHT) caused by 5ARIs, erectile and ejaculatory dysfunctions and loss of libido are reported (Hirshburg et al., 2016). Depression is also a side effect observed with 5ARIs treatment (Hirshburg et al., 2016). Nevertheless, a recent study reported an overall increase in depression with dutasteride occurring in 3.4 % of men investigated; hence, 96.6 % did not get depression and could benefit from dutasteride (Garcia-Argibay et al., 2022). A stratified analysis as a function of the duration of treatment, the longest time, >48 months, showed no significant increase in depression (Garcia-Argibay et al., 2022) compatible with long-term dutasteride treatment that we foresee for PD. Depression was increased with chronic finasteride treatment at all time points investigated (1–6 months, 7–12 months, 13–48 months, and > 48 months) (Garcia-Argibay et al., 2022). Hence, based on these observations in humans and the results in rodent models of PD, dutasteride shows better activity on DA systems and fewer side effects than finasteride in humans and should be favored. As shown in the present review, dutasteride is more effective at a lower dose than finasteride in animal models of PD.

It should be noted that studies reported here with rodent models of PD use higher doses of finasteride and dutasteride than those used in humans. This could be explained by the higher metabolism of rodents than humans. Moreover, finasteride and dutasteride are less effective in female than male rodents. Hence, 5ARIs should be proposed for men whereas women could benefit from other endocrine drugs such as progesterone and selective estrogen receptor modulators (SERM) like raloxifene.

Results reviewed here show that dutasteride is not neuroprotective in GDX male and female mice to model andropause and menopause. PD is a disease of aging starting around the age of 50 for the idiopathic disease that constitutes most cases, and it is around this age that women go into menopause. In men, andropause is progressive with a slow decline of

gonadal hormones, and only a few very old men will have reduced gonadal hormones, as modeled with GDX male mice. Therefore, it is expected that 5ARIs will be effective in most men with PD.

Neuroprotection and antidyskinetic activities of 5ARIs in animal models of PD suggest their repurposing for men with PD for gut dysfunction and to protect brain DA and inhibit dyskinesias. Moreover, 5ARIs could also reduce psychiatric symptoms in PD, as reported in case reports where finasteride reduces pathological gambling (Bortolato et al., 2012) and pramipexole-induced alterations in probability discounting (Floris et al., 2022). In treating benign essential blepharospasm, a case report showed that finasteride significantly attenuated the severity of dystonic symptoms (Bortolato et al., 2010). Pre-clinical studies and case reports support the need for further investigation of 5ARIs for PD treatment. However, finasteride and dutasteride are not yet tested in placebo-controlled studies likely because these drugs are already sold as generic, and thus no sponsor could be found to fund these studies. The other obstacle is that finasteride is only approved for use in men, which raises further problems with the new guidelines for clinical trials. Nevertheless, accumulating supportive animal studies on finasteride and dutasteride help identify mechanisms that can unveil novel neurosteroids-based therapies for the treatment of motor and non-motor symptoms of PD.

CRediT authorship contribution statement

Mélanie Bourque: Writing – original draft. **Marc Morissette:** Writing – review & editing. **Amandine Isenbrandt:** Writing – review & editing. **Silvia Giatti:** Writing – review & editing. **Roberto Cosimo Melcangi:** Writing – review & editing. **Manolo Carta:** Writing – review & editing. **Roberto Frau:** Writing – review & editing. **Marco Bortolato:** Writing – review & editing. **Denis Soulet:** Writing – review & editing. **Thérèse Di Paolo:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgment

This review was supported by grant from the Canadian Institutes for Health Research (CIHR) (506071).

References

Armstrong, M.J., Okun, M.S., 2020. Diagnosis and Treatment of Parkinson Disease: A Review. J. Am. Med. Assoc. 323, 548–560. https://doi.org/10.1001/jama.2019.22360.

Awogbindin, I.O., Ishola, I.O., St-Pierre, M.K., Carrier, M., Savage, J.C., Di Paolo, T., Tremblay, M., 2020. Remodeling microglia to a protective phenotype in Parkinson's disease? Neurosci. Lett. 735, 135164. https://doi.org/10.1016/j.neulet.2020.135164.

Baba, Y., Putzke, J.D., Whaley, N.R., Wszolek, Z.K., Uitti, R.J., 2005. Gender and the Parkinson's disease phenotype. J. Neurol. 252, 1201–1205. https://doi.org/10.1007/s00415-005-0835-7.

Bach, J.P., Ziegler, U., Deuschl, G., Dodel, R., Doblhammer-Reiter, G., 2011. Projected numbers of people with movement disorders in the years 2030 and 2050. Movement Disorders : Off. J. Movement Disorder Soc. 26, 2286–2290. https://doi.org/10.1002/mds.23878.

Barko, K., Shelton, M., Xue, X., Afriyie-Agyemang, Y., Puig, S., Freyberg, Z., Tseng, G.C., Logan, R.W., Seney, M.L., 2022. Brain region- and sex-specific transcriptional profiles of microglia. Front. Psych. 13, 945548. https://doi.org/10.3389/fpsyt.2022.945548.

Bellini, G., Benvenuti, L., Ippolito, C., Frosini, D., Segnani, C., Rettura, F., Pancetti, A., Bertani, L., D'Antongiovanni, V., Palermo, G., Del Prete, E., Antonioli, L., Nardini, V., Morganti, R., Pellegrini, C., Bernardini, N., Ceravolo, R., Fornai, M., Bellini, M., 2023. Intestinal histomorphological and molecular alterations in patients with Parkinson's disease. Eur. J. Neurol. 30, 3440–3450. https://doi.org/10.1111/ene.15607.

Bézard, E., Ferry, S., Mach, U., Stark, H., Leriche, L., Boraud, T., Gross, C., Sokoloff, P., 2003. Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. Nat. Med. 9, 762–767. https://doi.org/10.1038/nm875.

Bjornestad, A., Forsaa, E.B., Pedersen, K.F., Tysnes, O.B., Larsen, J.P., Alves, G., 2016. Risk and course of motor complications in a population-based incident Parkinson's disease cohort. Parkinsonism Relat. Disord. 22, 48–53. https://doi.org/10.1016/j.parkreldis.2015.11.007.

Bortolato, M., Frau, R., Orrù, M., Bourov, Y., Marrosu, F., Mereu, G., Devoto, P., Gessa, G. L., 2008. Antipsychotic-like properties of 5-alpha-reductase inhibitors. Neuropsychopharmacology 33, 3146–3156. https://doi.org/10.1038/npp.2008.39.

Bortolato, M., Cannas, A., Solla, P., Puligheddu, M., Muroni, A., Marrosu, F., 2010. Treatment of benign essential blepharospasm with finasteride: a case report. Clin. Neuropharmacol. 33, 207–208. https://doi.org/10.1097/WNF.0b013e3181dca96f.

Bortolato, M., Cannas, A., Solla, P., Bini, V., Puligheddu, M., Marrosu, F., 2012. Finasteride attenuates pathological gambling in patients with Parkinson disease. J. Clin. Psychopharmacol. 32, 424–425. https://doi.org/10.1097/JCP.0b013e3182549c2a.

Bourque, M., Dluzen, D.E., Di Paolo, T., 2012. Signaling pathways mediating the neuroprotective effects of sex steroids and SERMs in Parkinson's disease. Front. Neuroendocrinol. 33, 169–178. https://doi.org/10.1016/j.yfrne.2012.02.003.

Bourque, M., Morissette, M., Di Paolo, T., 2015. Neuroprotection in Parkinsonian-treated mice via estrogen receptor α activation requires G protein-coupled estrogen receptor 1. Neuropharmacology 95, 343–352. https://doi.org/10.1016/j.neuropharm.2015.04.006.

Bourque, M., Morissette, M., Al Sweidi, S., Caruso, D., Melcangi, R.C., Di Paolo, T., 2016. Neuroprotective Effect of Progesterone in MPTP-Treated Male Mice. Neuroendocrinology 103, 300–314. https://doi.org/10.1159/000438789.

Bourque, M., Grégoire, L., Patel, W., Dickens, D., Snodgrass, R., Di Paolo, T., 2022. AV-101, a Pro-Drug Antagonist at the NMDA Receptor Glycine Site, Reduces L-Dopa Induced Dyskinesias in MPTP Monkeys. Cells 11, 3530.

Bourque, M., Morissette, M., Soulet, D., Di Paolo, T., 2023. Impact of sex on neuroimmune contributions to Parkinson's disease. Brain Res. Bull. 199, 110668. https://doi.org/10.1016/j.brainresbull.2023.110668.

Bourque, M., Morissette, M., Di Paolo, T., 2024. Neuroactive steroids and Parkinson's disease: Review of human and animal studies. Neurosci. Biobehav. Rev. 156, 105479. https://doi.org/10.1016/j.neubiorev.2023.105479.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003a. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211. https://doi.org/10.1016/s0197-4580(02)00065-9.

Braak, H., Rüb, U., Gai, W.P., Del Tredici, K., 2003b. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J. Neural Transm. (Vienna) 110, 517–536. https://doi.org/10.1007/s00702-002-0808-2.

Calon, F., Rajput, A.H., Hornykiewicz, O., Bédard, P.J., Di Paolo, T., 2003. Levodopa-induced motor complications are associated with alterations of glutamate receptors in Parkinson's disease. Neurobiol. Dis. 14, 404–416. https://doi.org/10.1016/j.nbd.2003.07.003.

Cameron, K., Bartle, E., Roark, R., Fanelli, D., Pham, M., Pollard, B., Borkowski, B., Rhoads, S., Kim, J., Rocha, M., Kahlson, M., Kangala, M., Gentile, L., 2012. Neurosteroid binding to the amino terminal and glutamate binding domains of ionotropic glutamate receptors. Steroids 77, 774–779. https://doi.org/10.1016/j.steroids.2012.03.011.

Campanelli, F., Natale, G., Marino, G., Ghiglieri, V., Calabresi, P., 2022. Striatal glutamatergic hyperactivity in Parkinson's disease. Neurobiol. Dis. 168, 105697. https://doi.org/10.1016/j.nbd.2022.105697.

Cantagrel, V., Lefeber, D.J., Ng, B.G., Guan, Z., Silhavy, J.L., Bielas, S.L., Lehle, L., Hombauer, H., Adamowicz, M., Swiezewska, E., De Brouwer, A.P., Blümel, P., Sykut-Cegielska, J., Houliston, S., Swistun, D., Ali, B.R., Dobyns, W.B., Babovic-Vuksanovic, D., van Bokhoven, H., Wevers, R.A., Raetz, C.R., Freeze, H.H., Morava, E., Al-Gazali, L., Gleeson, J.G., 2010. SRD5A3 is required for converting polyprenol to dolichol and is mutated in a congenital glycosylation disorder. Cell 142, 203–217. https://doi.org/10.1016/j.cell.2010.06.001.

Carta, M., Björklund, A., 2018. The serotonergic system in L-DOPA-induced dyskinesia: pre-clinical evidence and clinical perspective. J. Neural Transm. (Vienna) 125, 1195–1202. https://doi.org/10.1007/s00702-018-1865-5.

Carta, M., Carlsson, T., Kirik, D., Björklund, A., 2007. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain 130, 1819–1833. https://doi.org/10.1093/brain/awm082.

Caruso, D., Pesaresi, M., Maschi, O., Giatti, S., Garcia-Segura, L.M., Melcangi, R.C., 2010. Effect of short-and long-term gonadectomy on neuroactive steroid levels in the central and peripheral nervous system of male and female rats. J. Neuroendocrinol. 22, 1137–1147. https://doi.org/10.1111/j.1365-2826.2010.02064.x.

Caruso, D., Pesaresi, M., Abbiati, F., Calabrese, D., Giatti, S., Garcia-Segura, L.M., Melcangi, R.C., 2013. Comparison of plasma and cerebrospinal fluid levels of neuroactive steroids with their brain, spinal cord and peripheral nerve levels in male and female rats. Psychoneuroendocrinology 38, 2278–2290. https://doi.org/10.1016/j.psyneuen.2013.04.016.

Castelli, M.P., Casti, A., Casu, A., Frau, R., Bortolato, M., Spiga, S., Ennas, M.G., 2013. Regional distribution of 5α-reductase type 2 in the adult rat brain: an immunohistochemical analysis. Psychoneuroendocrinology 38, 281–293. https://doi.org/10.1016/j.psyneuen.2012.06.008.

Cerri, S., Mus, L., Blandini, F., 2019. Parkinson's Disease in Women and Men: What's the Difference? J. Parkinsons Dis. 9, 501–515. https://doi.org/10.3233/jpd-191683.

Chagraoui, A., Di Giovanni, G., De Deurwaerdère, P., 2022. Neurobiological and Pharmacological Perspectives of D3 Receptors in Parkinson's Disease. Biomolecules 12. https://doi.org/10.3390/biom12020243.

Clark, R.V., Hermann, D.J., Cunningham, G.R., Wilson, T.H., Morrill, B.B., Hobbs, S., 2004. Marked Suppression of Dihydrotestosterone in Men with Benign Prostatic Hyperplasia by Dutasteride, a Dual 5α-Reductase Inhibitor. J. Clin. Endocrinol. Metab. 89, 2179–2184. https://doi.org/10.1210/jc.2003-030330.

Collaborators, G.N., 2019. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18, 459–480. https://doi.org/10.1016/s1474-4422(18)30499-x.

Colombo, D., Abbruzzese, G., Antonini, A., Barone, P., Bellia, G., Franconi, F., Simoni, L., Attar, M., Zagni, E., Haggiag, S., Stocchi, F., 2015. The "gender factor" in wearing-off among patients with Parkinson's disease: a post hoc analysis of DEEP study. ScientificWorldJournal 2015, 787451. https://doi.org/10.1155/2015/787451.

Conrad, A.T., Dittel, B.N., 2011. Taming of macrophage and microglial cell activation by microRNA-124. Cell Res. 21, 213–216. https://doi.org/10.1038/cr.2011.9.

Corsi, S., Scheggi, S., Pardu, A., Braccagni, G., Caruso, D., Cioffi, L., Diviccaro, S., Gentile, M., Fanni, S., Stancampiano, R., Gambarana, C., Melcangi, R.C., Frau, R., Carta, M., 2023. Pregnenolone for the treatment of L-DOPA-induced dyskinesia in Parkinson's disease. Exp. Neurol. 363, 114370. https://doi.org/10.1016/j.expneurol.2023.114370.

Côté, M., Poirier, A.A., Aubé, B., Jobin, C., Lacroix, S., Soulet, D., 2015. Partial depletion of the proinflammatory monocyte population is neuroprotective in the myenteric plexus but not in the basal ganglia in a MPTP mouse model of Parkinson's disease. Brain Behav. Immun. 46, 154–167. https://doi.org/10.1016/j.bbi.2015.01.009.

D'Astous, M., Mendez, P., Morissette, M., Garcia-Segura, L.M., Di Paolo, T., 2006. Implication of the phosphatidylinositol-3 kinase/protein kinase B signaling pathway in the neuroprotective effect of estradiol in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice. Mol. Pharmacol. 69, 1492–1498. https://doi.org/10.1124/mol.105.018671.

Devos, D., Lebouvier, T., Lardeux, B., Biraud, M., Rouaud, T., Pouclet, H., Coron, E., Bruley des Varannes, S., Naveilhan, P., Nguyen, J.M., Neunlist, M., and Derkinderen, P., 2013. Colonic inflammation in Parkinson's disease. Neurobiology of disease 50, 42-8. https://doi.org/10.1016/j.nbd.2012.09.007.

di Biase, L., Pecoraro, P.M., Carbone, S.P., Caminiti, M.L., Di Lazzaro, V., 2023. Levodopa-Induced Dyskinesias in Parkinson's Disease: An Overview on Pathophysiology, Clinical Manifestations, Therapy Management Strategies and Future Directions. J. Clin. Med. 12. https://doi.org/10.3390/jcm12134427.

di Michele, F., Longone, P., Romeo, E., Lucchetti, S., Brusa, L., Pierantozzi, M., Bassi, A., Bernardi, G., Stanzione, P., 2003. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol. Sci. 24, 172–173. https://doi.org/10.1007/s10072-003-0115-1.

Dluzen, D.E., 1996. Effects of testosterone upon MPTP-induced neurotoxicity of the nigrostriatal dopaminergic system of C57/B1 mice. Brain Res. 715, 113–118. https://doi.org/10.1016/0006-8993(95)01566-3.

Ekue, A., Boulanger, J.F., Morissette, M., Di Paolo, T., 2002. Lack of effect of testosterone and dihydrotestosterone compared to 17beta-oestradiol in 1-methyl-4-phenyl-1,2,3,6, tetrahydropyridine-mice. J. Neuroendocrinol. 14, 731–736. https://doi.org/10.1046/j.1365-2826.2002.00833.x.

Fanni, S., Scheggi, S., Rossi, F., Tronci, E., Traccis, F., Stancampiano, R., De Montis, M.G., Devoto, P., Gambarana, C., Bortolato, M., Frau, R., Carta, M., 2019. 5alpha-reductase inhibitors dampen L-DOPA-induced dyskinesia via normalization of dopamine D1-receptor signaling pathway and D1–D3 receptor interaction. Neurobiol. Dis. 121, 120–130. https://doi.org/10.1016/j.nbd.2018.09.018.

Floris, G., Scheggi, S., Pes, R., Bortolato, M., 2022. The steroidogenic inhibitor finasteride reverses pramipexole-induced alterations in probability discounting. Brain Res. Bull. 181, 157–166. https://doi.org/10.1016/j.brainresbull.2022.01.020.

Frau, R., Pillolla, G., Bini, V., Tambaro, S., Devoto, P., Bortolato, M., 2013. Inhibition of 5α-reductase attenuates behavioral effects of D1-, but not D2-like receptor agonists in C57BL/6 mice. Psychoneuroendocrinology 38, 542–551. https://doi.org/10.1016/j.psyneuen.2012.07.014.

Frau, R., Mosher, L.J., Bini, V., Pillolla, G., Pes, R., Saba, P., Fanni, S., Devoto, P., Bortolato, M., 2016. The neurosteroidogenic enzyme 5α-reductase modulates the role of D1 dopamine receptors in rat sensorimotor gating. Psychoneuroendocrinology 63, 59–67. https://doi.org/10.1016/j.psyneuen.2015.09.014.

Frau, R., Bini, V., Soggiu, A., Scheggi, S., Pardu, A., Fanni, S., Roncada, P., Puligheddu, M., Marrosu, F., Caruso, D., Devoto, P., Bortolato, M., 2017a. The Neurosteroidogenic Enzyme 5α-Reductase Mediates Psychotic-Like Complications of Sleep Deprivation. Neuropsychopharmacology 42, 2196–2205. https://doi.org/10.1038/npp.2017.13.

Frau, R., Savoia, P., Fanni, S., Fiorentini, C., Fidalgo, C., Tronci, E., Stancampiano, R., Meloni, M., Cannas, A., Marrosu, F., Bortolato, M., Devoto, P., Missale, C., Carta, M., 2017b. The 5-alpha reductase inhibitor finasteride reduces dyskinesia in a rat model of Parkinson's disease. Exp. Neurol. 291, 1–7. https://doi.org/10.1016/j.expneurol.2017.01.012.

Frentzel, D., Judanin, G., Borozdina, O., Klucken, J., Winkler, J., Schlachetzki, J.C.M., 2017. Increase of Reproductive Life Span Delays Age of Onset of Parkinson's Disease. Front. Neurol. 8, 397. https://doi.org/10.3389/fneur.2017.00397.

Garcia-Argibay, M., Hiyoshi, A., Fall, K., Montgomery, S., 2022. Association of 5α-Reductase Inhibitors With Dementia, Depression, and Suicide. JAMA Netw. Open 5, e2248135.

Giatti, S., Diviccaro, S., Garcia-Segura, L.M., Melcangi, R.C., 2019a. Sex differences in the brain expression of steroidogenic molecules under basal conditions and after gonadectomy. J. Neuroendocrinol. 31, e12736.

Giatti, S., Garcia-Segura, L.M., Barreto, G.E., Melcangi, R.C., 2019b. Neuroactive steroids, neurosteroidogenesis and sex. Prog. Neurobiol. 176, 1–17. https://doi.org/10.1016/j.pneurobio.2018.06.007.

Giatti, S., Diviccaro, S., Falvo, E., Garcia-Segura, L.M., Melcangi, R.C., 2020. Physiopathological role of the enzymatic complex 5α-reductase and 3α/β-hydroxysteroid oxidoreductase in the generation of progesterone and testosterone neuroactive metabolites. Front. Neuroendocrinol. 57, 100836. https://doi.org/10.1016/j.yfrne.2020.100836.

Gillies, G.E., Murray, H.E., Dexter, D., McArthur, S., 2004. Sex dimorphisms in the neuroprotective effects of estrogen in an animal model of Parkinson's disease. Pharmacol. Biochem. Behav 78, 513–522. https://doi.org/10.1016/j.pbb.2004.04.022.

Gomez-Mancilla, B., Bédard, P.J., 1992. Effect of estrogen and progesterone on L-dopa induced dyskinesia in MPTP-treated monkeys. Neurosci. Lett. 135, 129–132. https://doi.org/10.1016/0304-3940(92)90152-w.

Group, G.B.D.N.D.C., 2017. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol 16, 877-897. https://doi.org/10.1016/S1474-4422(17)30299-5.

Guneykaya, D., Ivanov, A., Hernandez, D.P., Haage, V., Wojtas, B., Meyer, N., Maricos, M., Jordan, P., Buonfiglioli, A., Gielniewski, B., Ochocka, N., Cömert, C., Friedrich, C., Artiles, L.S., Kaminska, B., Mertins, P., Beule, D., Kettenmann, H., Wolf, S.A., 2018. Transcriptional and Translational Differences of Microglia from Male and Female Brains. Cell Rep. 24, 2773–2783.e6. https://doi.org/10.1016/j.celrep.2018.08.001.

Gupta, A.K., Talukder, M., and Williams, G., 2024. Emerging and traditional 5-α reductase inhibitors and androgen receptor antagonists for male androgenetic alopecia. Expert Opin Emerg Drugs1-11. https://doi.org/10.1080/14728214.2024.2346590.

Haaxma, C.A., Bloem, B.R., Borm, G.F., Oyen, W.J., Leenders, K.L., Eshuis, S., Booij, J., Dluzen, D.E., Horstink, M.W., 2007. Gender differences in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 78, 819–824. https://doi.org/10.1136/jnnp.2006.103788.

Hirsch, L., Jette, N., Frolkis, A., Steeves, T., Pringsheim, T., 2016. The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 46, 292–300. https://doi.org/10.1159/000445751.

Hirshburg, J.M., Kelsey, P.A., Therrien, C.A., Gavino, A.C., Reichenberg, J.S., 2016. Adverse Effects and Safety of 5-alpha Reductase Inhibitors (Finasteride, Dutasteride): A Systematic Review. J. Clin. Aesthet. Dermatol. 9, 56–62.

Isenbrandt, A., Morissette, M., Bourque, M., Lamontagne-Proulx, J., Coulombe, K., Soulet, D., Di Paolo, T., 2021. Effect of sex and gonadectomy on brain MPTP toxicity and response to dutasteride treatment in mice. Neuropharmacology 201, 108784. https://doi.org/10.1016/j.neuropharm.2021.108784.

Isenbrandt, A., Coulombe, K., Morissette, M., Bourque, M., Lamontagne-Proulx, J., Di Paolo, T., Soulet, D., 2023. Three-Dimensional Analysis of Sex- and Gonadal Status-Dependent Microglial Activation in a Mouse Model of Parkinson's Disease. Pharmaceuticals (basel, Switzerland) 16. https://doi.org/10.3390/ph16020152.

Jankovic, J., Tan, E.K., 2020. Parkinson's disease: etiopathogenesis and treatment. J. Neurol. Neurosurg. Psychiatry 91, 795–808. https://doi.org/10.1136/jnnp-2019-322338.

Jurado-Coronel, J.C., Cabezas, R., Ávila Rodríguez, M.F., Echeverria, V., García-Segura, L.M., Barreto, G.E., 2018. Sex differences in Parkinson's disease: Features on clinical symptoms, treatment outcome, sexual hormones and genetics. Front. Neuroendocrinol. 50, 18–30. https://doi.org/10.1016/j.yfrne.2017.09.002.

Kobylecki, C., Cenci, M.A., Crossman, A.R., Ravenscroft, P., 2010. Calcium-permeable AMPA receptors are involved in the induction and expression of l-DOPA-induced dyskinesia in Parkinson's disease. J. Neurochem. 114, 499–511. https://doi.org/10.1111/j.1471-4159.2010.06776.x.

Kwon, D.K., Kwatra, M., Wang, J., Ko, H.S., 2022. Levodopa-Induced Dyskinesia in Parkinson's Disease: Pathogenesis and Emerging Treatment Strategies. Cells 11. https://doi.org/10.3390/cells11233736.

Litim, N., Bourque, M., Al Sweidi, S., Morissette, M., Di Paolo, T., 2015. The 5α-reductase inhibitor Dutasteride but not Finasteride protects dopamine neurons in the MPTP mouse model of Parkinson's disease. Neuropharmacology 97, 86–94. https://doi.org/10.1016/j.neuropharm.2015.05.015.

Litim, N., Morissette, M., Caruso, D., Melcangi, R.C., Di Paolo, T., 2017. Effect of the 5α-reductase enzyme inhibitor dutasteride in the brain of intact and parkinsonian mice. J. Steroid Biochem. Mol. Biol. 174, 242–256. https://doi.org/10.1016/j.jsbmb.2017.09.021.

Loughlin, K.R., 2021. The clinical applications of five-alpha reductase inhibitors. Can. J. Urol. 28, 10584–10588.

Luchetti, S., Bossers, K., Frajese, G.V., Swaab, D.F., 2010. Neurosteroid biosynthetic pathway changes in substantia nigra and caudate nucleus in Parkinson's disease. Brain Pathol. 20, 945–951. https://doi.org/10.1111/j.1750-3639.2010.00396.x.

Luchetti, S., Liere, P., Pianos, A., Verwer, R.W.H., Sluiter, A., Huitinga, I., Schumacher, M., Swaab, D.F., Mason, M.R.J., 2023. Disease stage-dependent changes in brain levels and neuroprotective effects of neuroactive steroids in Parkinson's disease. Neurobiol. Dis. 183, 106169. https://doi.org/10.1016/j.nbd.2023.106169.

Marcellino, D., Ferré, S., Casadó, V., Cortés, A., Le Foll, B., Mazzola, C., Drago, F., Saur, O., Stark, H., Soriano, A., Barnes, C., Goldberg, S.R., Lluis, C., Fuxe, K., Franco, R., 2008. Identification of dopamine D1–D3 receptor heteromers. Indications for a role of synergistic D1–D3 receptor interactions in the striatum. J. Biol. Chem. 283, 26016–26025. https://doi.org/10.1074/jbc.M710349200.

Matsui, H., Takahashi, R., 2024. Current trends in basic research on Parkinson's disease: from mitochondria, lysosome to α-synuclein. J. Neural Transm. (Vienna). https://doi.org/10.1007/s00702-024-02774-2.

Melcangi, R.C., Garcia-Segura, L.M., Mensah-Nyagan, A.G., 2008. Neuroactive steroids: state of the art and new perspectives. Cell. Mol. Life Sci. 65, 777–797. https://doi.org/10.1007/s00018-007-7403-5.

Melcangi, R.C., Caruso, D., Levandis, G., Abbiati, F., Armentero, M.T., Blandini, F., 2012. Modifications of neuroactive steroid levels in an experimental model of nigrostriatal degeneration: potential relevance to the pathophysiology of Parkinson's disease. J. Molecular Neuroscience : MN 46, 177–183. https://doi.org/10.1007/s12031-011-9570-y.

Mellone, M., Zianni, E., Stanic, J., Campanelli, F., Marino, G., Ghiglieri, V., Longhi, A., Thiolat, M.L., Li, Q., Calabresi, P., Bezard, E., Picconi, B., Di Luca, M., Gardoni, F., 2019. NMDA receptor GluN2D subunit participates to levodopa-induced dyskinesia pathophysiology. Neurobiol. Dis. 121, 338–349. https://doi.org/10.1016/j.nbd.2018.09.021.

Miller, D.B., Ali, S.F., O'Callaghan, J.P., Laws, S.C., 1998. The impact of gender and estrogen on striatal dopaminergic neurotoxicity. Ann. N. Y. Acad. Sci. 844, 153–165.

Morin, N., Morissette, M., Grégoire, L., Rajput, A., Rajput, A.H., Di Paolo, T., 2015. Contribution of brain serotonin subtype 1B receptors in levodopa-induced motor complications. Neuropharmacology 99, 356–368. https://doi.org/10.1016/j.neuropharm.2015.08.002.

Muroni, A., Paba, S., Puligheddu, M., Marrosu, F., Bortolato, M., 2011. A preliminary study of finasteride in Tourette syndrome. Movement Disorders : Official Journal of the Movement Disorder Society 26, 2146–2147. https://doi.org/10.1002/mds.23810.

Murray, H.E., Pillai, A.V., McArthur, S.R., Razvi, N., Datla, K.P., Dexter, D.T., Gillies, G. E., 2003. Dose- and sex-dependent effects of the neurotoxin 6-hydroxydopamine on the nigrostriatal dopaminergic pathway of adult rats: differential actions of estrogen in males and females. Neuroscience 116, 213–222. https://doi.org/10.1016/s0306-4522(02)00578-x.

Nitkowska, M., Tomasiuk, R., Czyzyk, M., Friedman, A., 2015. Prolactin and sex hormones levels in males with Parkinson's disease. Acta Neurol. Scand. 131, 411–416. https://doi.org/10.1111/ane.12334.

Okun, M.S., Crucian, G.P., Fischer, L., Walter, B.L., Testa, C.M., Vitek, J.L., DeLong, M.R., Hanfelt, J., Huang, X., 2004. Testosterone deficiency in a Parkinson's disease clinic: results of a survey. J. Neurol. Neurosurg. Psychiatry 75, 165–166.

Ouattara, B., Belkhir, S., Morissette, M., Dridi, M., Samadi, P., Grégoire, L., Meltzer, L.T., Di Paolo, T., 2009. Implication of NMDA receptors in the antidyskinetic activity of cabergoline, CI-1041, and Ro 61–8048 in MPTP monkeys with levodopa-induced dyskinesias. Journal of Molecular Neuroscience : MN 38, 128–142. https://doi.org/10.1007/s12031-008-9137-8.

Ouattara, B., Hoyer, D., Grégoire, L., Morissette, M., Gasparini, F., Gomez-Mancilla, B., Di Paolo, T., 2010. Changes of AMPA receptors in MPTP monkeys with levodopa-induced dyskinesias. Neuroscience 167, 1160–1167. https://doi.org/10.1016/j.neuroscience.2010.03.022.

Ouattara, B., Grégoire, L., Morissette, M., Gasparini, F., Vranesic, I., Bilbe, G., Johns, D. R., Rajput, A., Hornykiewicz, O., Rajput, A.H., Gomez-Mancilla, B., Di Paolo, T., 2011. Metabotropic glutamate receptor type 5 in levodopa-induced motor complications. Neurobiol. Aging 32, 1286–1295. https://doi.org/10.1016/j.neurobiolaging.2009.07.014.

Poirier, A.A., Côté, M., Bourque, M., Morissette, M., Di Paolo, T., Soulet, D., 2016. Neuroprotective and immunomodulatory effects of raloxifene in the myenteric plexus of a mouse model of Parkinson's disease. Neurobiol. Aging 48, 61–71. https://doi.org/10.1016/j.neurobiolaging.2016.08.004.

Poirier, A.A., Côté, M., Jarras, H., Litim, N., Lamontagne-Proulx, J., Al-Sweidi, S., Morissette, M., Lachhab, A., Pelletier, M., Di Paolo, T., Soulet, D., 2022. Peripheral Neuroprotective and Immunomodulatory Effects of 5α-Reductase Inhibitors in Parkinson's Disease Models. Front. Pharmacol. 13, 898067. https://doi.org/10.3389/fphar.2022.898067.

Prashanth, L.K., Fox, S., Meissner, W.G., 2011. l-Dopa-induced dyskinesia-clinical presentation, genetics, and treatment. Int. Rev. Neurobiol. 98, 31–54. https://doi.org/10.1016/b978-0-12-381328-2.00002-x.

Rajput, A.H., Rajput, A., Lang, A.E., Kumar, R., Uitti, R.J., Galvez-Jimenez, N., 1998. New use for an old drug: amantadine benefits levodopa-induced dyskinesia. Movement Disorders : Official Journal of the Movement Disorder Society 13, 851. https://doi.org/10.1002/mds.870130520.

Riahi, G., Morissette, M., Parent, M., Di Paolo, T., 2011. Brain 5-HT(2A) receptors in MPTP monkeys and levodopa-induced dyskinesias. Eur. J. Neurosci. 33, 1823–1831. https://doi.org/10.1111/j.1460-9568.2011.07675.x.

Rossi, A., Berger, K., Chen, H., Leslie, D., Mailman, R.B., Huang, X., 2018. Projection of the prevalence of Parkinson's disease in the coming decades: Revisited. Movement Disorders : Official Journal of the Movement Disorder Society 33, 156–159. https://doi.org/10.1002/mds.27063.

Sánchez-Ferro, Á., Rábano, A., Catalán, M.J., Rodríguez-Valcárcel, F.C., Fernández Díez, S., Herreros-Rodríguez, J., García-Cobos, E., Álvarez-Santullano, M.M., López-Manzanares, L., Mosqueira, A.J., Vela Desojo, L., López-Lozano, J.J., López-Valdés, E., Sánchez-Sánchez, R., Molina-Arjona, J.A., 2015. In vivo gastric detection of α-synuclein inclusions in Parkinson's disease. Movement Disorders : Official Journal of the Movement Disorder Society 30, 517–524. https://doi.org/10.1002/mds.25988.

Savica, R., Grossardt, B.R., Bower, J.H., Ahlskog, J.E., Rocca, W.A., 2013. Risk factors for Parkinson's disease may differ in men and women: an exploratory study. Horm. Behav. 63, 308–314. https://doi.org/10.1016/j.yhbeh.2012.05.013.

Schverer, M., Lanfumey, L., Baulieu, E.E., Froger, N., Villey, I., 2018. Neurosteroids: non-genomic pathways in neuroplasticity and involvement in neurological diseases. Pharmacol. Ther. 191, 190–206. https://doi.org/10.1016/j.pharmthera.2018.06.011.

Shin, E., Rogers, J.T., Devoto, P., Björklund, A., Carta, M., 2014. Noradrenaline neuron degeneration contributes to motor impairments and development of L-DOPA-induced dyskinesia in a rat model of Parkinson's disease. Exp. Neurol. 257, 25–38. https://doi.org/10.1016/j.expneurol.2014.04.011.

Spigolon, G., Fisone, G., 2018. Signal transduction in L-DOPA-induced dyskinesia: from receptor sensitization to abnormal gene expression. J. Neural Transm. (Vienna) 125, 1171–1186. https://doi.org/10.1007/s00702-018-1847-7.

Thomasi, B., Valdetaro, L., Gulbransen, B., Tavares-Gomes, A.L., 2024. Neuroimmune Connectomes in the Gut and Their Implications in Parkinson's Disease. Mol. Neurobiol. 61, 2081–2098. https://doi.org/10.1007/s12035-023-03679-z.

Twelves, D., Perkins, K.S., Counsell, C., 2003. Systematic review of incidence studies of Parkinson's disease. Movement Disorders : Official Journal of the Movement Disorder Society 18, 19–31. https://doi.org/10.1002/mds.10305.

Uemura, M., Tamura, K., Chung, S., Honma, S., Okuyama, A., Nakamura, Y., Nakagawa, H., 2008. Novel 5 alpha-steroid reductase (SRD5A3, type-3) is overexpressed in hormone-refractory prostate cancer. Cancer Sci. 99, 81–86. https://doi.org/10.1111/j.1349-7006.2007.00656.x.

Visanji, N.P., Fox, S.H., Johnston, T., Reyes, G., Millan, M.J., Brotchie, J.M., 2009. Dopamine D3 receptor stimulation underlies the development of L-DOPA-induced dyskinesia in animal models of Parkinson's disease. Neurobiol. Dis. 35, 184–192. https://doi.org/10.1016/j.nbd.2008.11.010.

Wang, T., Sun, Y., Dettmer, U., 2023. Astrocytes in Parkinson's Disease: From Role to Possible Intervention. Cells 12. https://doi.org/10.3390/cells12192336.